PATENT COOPERATION TREATY

MAY 2 3 2003

PCT

TECH CENTER 1600/2900

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference USV340013514	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB00/01404	International filing date *(day/month/year)* 02 OCTOBER 2000	Priority date *(day/month/year)* NONE
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant USV LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   [✓] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   I [X] Basis of the report

   II [ ] Priority

   III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV [ ] Lack of unity of invention

   V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI [ ] Certain documents cited

   VII [ ] Certain defects in the international application

   VIII [ ] Certain observations on the international application

Date of submission of the demand 25 APRIL 2002	Date of completion of this report 26 SEPTEMBER 2002
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer LILIANA DI NOLA-BARON Telephone No. (703) 308-1234

Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/IB00/01404

I. Basis of the report

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-6, 8-13, as originally filed
pages 7, filed with the demand
pages NONE, filed with the letter of

[X] the claims:
pages 15, as originally filed
pages 14, 14(a), as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/IB00/01404

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-14	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-14	YES
	Claims	NONE	NO
Industrial Applicability (IA)	Claims	1-14	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-14 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest a monolithic composition of metformin hydrochloride comprising a hydrophobic polymer, and a process for forming said composition.

The claims find industrial applicability in the medical field for the treatment of noninsulin dependent diabetes mellitus.

---------- NEW CITATIONS ----------

NONE

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): A01N 37/52; A61K 47/30, 9/20, 9/22, 9/28 and US Cl.: 514/635, 772.3; 424/464, 465, 468, 474

Time(Hrs)	% Release
1	38 – 45%
2	50 – 55 %
3	62 – 68 %
4	70 – 75 %
5	80 – 85 %
6	85 – 90 %
7	91 – 95 %
8	96 – 100 %

Example 1 :

225 gm of stearic acid was melted at 70°C temperature. 1000 gm metformin hydrochloride was heated to 70°C in a jacketed rapid mixer granulator and granulated with above melted stearic acid at 70°C temperature. After granulation the granulate mass was mixed continuously with gradual cooling to room temperature.

60 gm of shellac and 25 gm of polyvinyl pyrollidone were dissolved in 150 gm of isopropyl alcohol. This solution was gradually added to above metformin stearic acid granulate and mixed till dough mass formed. The resulting dough mass was dried at 45°C for 2 hours and then sized through 2.4 mm screen to break the agglomerates. These sized granules (1310 gm) were blended with 4.0 gm of colloidal silicone dioxide and 8.0 gm of magnesium stearate and compressed into capsule shape oval tablets of each containing 1000 mg of metformin hydrochloride.

CLAIMS :

1. A monolithic sustained release composition, comprising a formulation that includes an active substance and a hydrophobic material, the active substance being metformin hydrochloride, the formulation being configured to exhibit in-vitro drug release characteristics of the metformin hydrochloride while in gastric fluid having a pH of 1.2 for a first hour and then in phosphate buffer having a pH of 6.8, the in-vitro drug release characteristics after the first, second, third, fourth, fifth, sixth, seventh and eighth hours being 38 - 45 % release by the first hour, 50-56 % release by the second hour, 62-68 % release by the third hour, 70-75 % release by the fourth hour, 80 - 85% release by the sixth hour, 85 - 90 % release by the seventh hour, 91 -95 % release by the eighth hour and 96-100 % release by the eighth hour.

2. Composition of claim 1, wherein the sustained release dose for metformin hydrochloride is at least 1000 mg.

3. Composition of claim 1, wherein at least 74 % by weight of the composition is metformin hydrochloride.

4. The pharmaceutical formulation as defined in claim 1, wherein the hydrophobic polymer and or hydrophobic material is selected from the group consisting of Fatty acids, Fatty alcohols, Fatty acid esters, Hydrogenated oils,

waxes and natural resins.

5. Composition of claim 4, wherein the hydrophobic polymer and or hydrophobic material comprises stearic acid, glyceryl monostearate, glyceryl behenate, glyceryl palmitostearate, glyceryl monooleate, microcrystalline wax, stearyl alcohol, cetyl alcohol, cetostearyl alcohol, hydrogenated castor oil, tristearin, shellac, rosin, polyvinyl chloride powder, polyethylene powder, and the like.

6. Composition of claim 1, further comprising about 3 to 10% by weight binder, up to 0.5 to 1.5% by weight glidant and up to 0.5 to 1.0% by weight of the lubricant.

7. Composition of claim 1, wherein pharmaceutical composition is tablet.

PATENT COOPERATION TREATY 2872

From the INTERNATIONAL SEARCHING AUTHORITY

09/857,877

To: SURESH KUMAR GIDWANI
COBRIN & GITTES
LEXINGTON AVENUE
NEW YORK, NY 10022

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference USV340013514	Date of Mailing *(day/month/year)* 09 MAY 2001
International application No. PCT/IB00/01404	**FOR FURTHER ACTION** **See paragraphs 1 and 4 below**
Applicant USV LIMITED	International filing date *(day/month/year)* 02 OCTOBER 2000

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

RECEIVED
AUG - 2 2001
TECHNOLOGY CENTER 2800

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer LILIANA DI NOLA-BARO TERRY J. DEY PARALEGAL SPECIALIST TECHNOLOGY CENTER 1600 Telephone No. (703) 308-1234

Form PCT/ISA/220 (July 1998) ☆ *(See notes on accompanying sheet)*

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confounded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It should not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

In what language ?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

Consequence if a demand for international preliminary examination has already been filed ?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase ?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When ? **Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).**

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;
(ii) the claim is cancelled;
(iii) the claim is new;
(iv) the claim replaces one or more claims as filed;
(v) the claim is the result of the division of a claim as filed.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference USV340013514	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/IB00/01404	International filing date *(day/month/year)* 02 OCTOBER 2000	(Earliest) Priority Date *(day/month/year)* NONE
Applicant USV LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:
   [ ] contained in the international application in written form.
   [ ] filed together with the international application in computer readable form.
   [ ] furnished subsequently to this Authority in written form.
   [ ] furnished subsequently to this Authority in computer readable form.
   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has b een furnished.
2. [ ] **Certain claims were found unsearchable** (See Box I).
3. [ ] **Unity of invention is lacking** (See Box II).
4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:
5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the **drawings** to be published with the abstract is Figure No. _____
   [ ] as suggested by the applicant.
   [ ] because the applicant failed to suggest a figure.
   [ ] because this figure better characterizes the invention.
   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB00/01404

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A01N 37/52; A61K 47/30, 9/20, 9/22, 9/28
US CL : 514/635, 772.3; 424/464, 465, 468, 474

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/635, 772.3; 424/464, 465, 468, 474

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/47128 A1 (BRISTOL-MYERS SQUIBB COMPANY) 23 September 1999, See entire document.	1-14
Y	US 5,922,769 A (BARELLI et al.) 13 July 1999, See entire document.	1-14
Y	US 6,011,049 A (WHITCOMB) 04 January 2000, See entire document.	1-14
Y	US 6,099,859 A (CHENG et al.) 08 August 2000, See entire document.	1-14
Y	US 6,099,862 A (CHEN et al.) 08 August 2000, See entire document.	1-14
Y	US 6,117,451 A (KUMAR) 12 September 2000, See entire document.	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
16 JANUARY 2001	09MAY2001

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	LILIANA DI NOLA-BARON TERRY J. DEY PARALEGAL SPECIALIST TECHNOLOGY CENTER 1600
Facsimile No. (703) 305-3230	Telephone No. (703) 308-12[illegible]

Form PCT/ISA/210 (second sheet) (July 1998) ☆

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* USV340013514

Box No. I TITLE OF INVENTION

SUSTAINED RELEASE PHARMACEUTICAL COMPOSITIONS CONTAINING METFORMIN AND METHOD

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

USV LIMITED
B.S.D. Marg (Govandi Station Road) Govandi,
Mumbai - 400 088
India

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: India

State *(that is, country)* of residence: India

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Gidwani, Suresh Kumar
B.S.D. Marg (Govandi Station Road) Govandi,
Mumbai - 400 088
India

This person is:

☐ applicant only

☐ applicant and inventor

☒ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: India

State *(that is, country)* of residence: India

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☐ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Cobrin & Gittes
Lexington Avenue
New York, New York 10022
US

Hess, Robert
Cobrin, Peter
Gittes, Marvin
Adler, Michael

Lehrer, Richard
Denenberg, David
Russ, Lawrence

Telephone No. (212) 486-4000

Facsimile No. (212) 486-4007

Teleprinter No.

☒ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Singnurkar, Purushottam
B.S.D. Marg (Govandi Station Road) Govandi,
Mumbai - 400 088
India

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☒ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: India

State *(that is, country)* of residence: India

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Tewari, Prashant Kumar
B.S.D. Marg (Govandi Station Road) Govandi,
Mumbai - 400 088
India

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☒ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: India

State *(that is, country)* of residence: India

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☑ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **MZ** Mozambique, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☑ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☑ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☑ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*

☑ **AE** United Arab Emirates
☑ **AG** Antigua and Barbuda
☑ **AL** Albania .....
☑ **AM** Armenia .....
☑ **AT** Austria .....
☑ **AU** Australia .....
☑ **AZ** Azerbaijan
☑ **BA** Bosnia and Herzegovina .....
☑ **BB** Barbados
☑ **BG** Bulgaria .....
☑ **BR** Brazil .....
☑ **BY** Belarus .....
☑ **BZ** Belize
☑ **CA** Canada
☑ **CH and LI** Switzerland and Liechtenstein
☑ **CN** China .....
☑ **CR** Costa Rica .....
☑ **CU** Cuba .....
☑ **CZ** Czech Republic .....
☑ **DE** Germany .....
☑ **DK** Denmark .....
☑ **DM** Dominica
☑ **DZ** Algeria .....
☑ **EE** Estonia .....
☑ **ES** Spain .....
☑ **FI** Finland .....
☑ **GB** United Kingdom
☑ **GD** Grenada
☑ **GE** Georgia .....
☑ **GH** Ghana .....
☑ **GM** Gambia
☑ **HR** Croatia .....
☑ **HU** Hungary .....
☑ **ID** Indonesia
☑ **IL** Israel .....
☑ **IN** India .....
☑ **IS** Iceland
☑ **JP** Japan .....
☑ **KE** Kenya .....
☑ **KG** Kyrgyzstan .....
☑ **KP** Democratic People's Republic of Korea .....
☑ **KR** Republic of Korea .....
☑ **KZ** Kazakhstan .....
☑ **LC** Saint Lucia
☑ **LK** Sri Lanka
☑ **LR** Liberia
☑ **LS** Lesotho .....
☑ **LT** Lithuania
☑ **LU** Luxembourg
☑ **LV** Latvia
☑ **MA** Morocco .....
☑ **MD** Republic of Moldova .....
☑ **MG** Madagascar .....
☑ **MK** The former Yugoslav Republic of Macedonia .....
☑ **MN** Mongolia
☑ **MW** Malawi .....
☑ **MX** Mexico .....
☑ **MZ** Mozambique
☑ **NO** Norway
☑ **NZ** New Zealand .....
☑ **PL** Poland .....
☑ **PT** Portugal .....
☑ **RO** Romania
☑ **RU** Russian Federation .....
☑ **SD** Sudan
☑ **SE** Sweden
☑ **SG** Singapore
☑ **SI** Slovenia .....
☑ **SK** Slovakia .....
☑ **SL** Sierra Leone .....
☑ **TJ** Tajikistan .....
☑ **TM** Turkmenistan .....
☑ **TR** Turkey .....
☑ **TT** Trinidad and Tobago .....
☑ **TZ** United Republic of Tanzania
☑ **UA** Ukraine .....
☑ **UG** Uganda .....
☑ **US** United States of America .....
☑ **UZ** Uzbekistan .....
☑ **VN** Viet Nam .....
☑ **YU** Yugoslavia .....
☑ **ZA** South Africa .....
☑ **ZW** Zimbabwe .....

Check-box reserved for designating States which have become party to the PCT after issuance of this sheet:

☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1)				
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / US

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 4
description (excluding sequence listing part)	: 13
claims	: 2
abstract	: 1
drawings	: 0
sequence listing part of description	:
Total number of sheets	: 19

This international application is **accompanied by** the item(s) marked below:

1. ☑ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☑ other *(specify)*: cheque

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Vilas Nagare
General Manager
USV Limited

USV LIMITED.

Authorised Signatory,

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	☐ received:
4. Date of timely receipt of the required corrections under PCT Article 11(2):	☐ not received:
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference USV340013514

Applicant

USV LIMITED

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . 200 T

2. SEARCH FEE . . . . . 700 S

International search to be carried out by US

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 19 sheets.

first 30 sheets 455 b1

____ x ____ = 0 b2

remaining sheets additional amount

Add amounts entered at b1 and b2 and enter total at B . . . . 455 B

Designation Fees

The international application contains 87 designations.

8 x 105 = 840 D

number of designation fees payable *(maximum 8)* amount of designation fee

Add amounts entered at B and D and enter total at I . . . . . 1295 I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . P

5. TOTAL FEES PAYABLE 2195

Add amounts entered at T, S, I and P, and enter total in the TOTAL box TOTAL

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☐ authorization to charge deposit account (see below)	☐ bank draft	☐ coupons
☒ cheque	☐ cash	☐ other *(specify)*:
☐ postal money order	☐ revenue stamps	

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ _____

☐ is hereby authorized to charge the total fees indicated above to my deposit account.

☐ *(this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

Deposit Account No. Date *(day/month/year)* Signature

See Notes to the fee calculation sheet

Copy for the designated Office (DO/US) PCT/IB00/01404

PATENT COOPERATION TREATY

9/857071

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

GIBBONS, Del Deo, Dolan,
Griffinger & Vecchione
750 Lexington Avenue, 21st Floor
New York, NY 10022
ETATS-UNIS D'AMERIQUE

RECEIVED
JUN 20 2002
TECH CENTER 1600/2900

Date of mailing (day/month/year) 10 May 2002 (10.05.02)	
Applicant's or agent's file reference USV340013514	**IMPORTANT NOTIFICATION**
International application No. PCT/IB00/01404	**International filing date** (day/month/year) 02 October 2000 (02.10.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
GIBBONS, Del Deo, Dolan, Griffinger & Vecchione 750 Lexington Avenue, 21st Floor New York, NY 10022 U.S.A	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
Address for correspondence

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Ki-Nam HA Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994) 004847817

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
United States of America

in its capacity as elected Office

Date of mailing (day/month/year) 27 November 2002 (27.11.02)	
International application No. PCT/IB00/01404	**Applicant's or agent's file reference** USV340013514
International filing date (day/month/year) 02 October 2000 (02.10.00)	**Priority date** (day/month/year)
Applicant GIDWANI, Suresh, Kumar et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

25 April 2002 (25.04.02)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Zakaria EL KHODARY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

09185707715040

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 April 2002 (11.04.2002)

PCT

(10) International Publication Number
WO 02/28181 A1

(51) International Patent Classification[7]: A01N 37/52, A61K 47/30, 9/20, 9/22, 9/28

(21) International Application Number: PCT/IB00/01404

(22) International Filing Date: 2 October 2000 (02.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: **USV LIMITED** [IN/IN]; B.S.D. Marg (Govandi Station Road) Govandi, Mumbai 400 088 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GIDWANI, Suresh, Kumar** [IN/IN]; B.S.D. Marg (Govandi Station Road) Govandi, Mumbai 400 088 (IN). **SINGNURKAR, Purushottam** [IN/IN]; B.S.D. Marg (Govandi Station Road) Govandi, Mumbai 400 088 (IN). **TEWARI, Prashant, Kumar** [IN/IN]; B.S.D. Marg (Govandi Station Road) Govandi, Mumbai 400 088 (IN).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/28181 A1

(54) **Title:** SUSTAINED RELEASE PHARMACEUTICAL COMPOSITIONS CONTAINING METFORMIN AND METHOD OF ITS PRODUCTION

(57) **Abstract:** Monolithic pharmaceutical composition containing metformin hydrophobic polymer and/or other hydrophobic material. Process of producing a sustained release of the composition that includes granulating metformin hydrochloride and hydrophobic polymer and/or other hydrophobic material by hot melt granulation or by extrusion and drying the granulated product.

SUSTAINED RELEASE PHARMACEUTICAL COMPOSITIONS CONTAINING METFORMIN AND METHOD OF ITS PRODUCTION

Field of the Invention

The present invention relates to sustained release pharmaceutical preparations containing metformin hydrochloride which provides sustained release of metformin hydrochloride over a prolong period of time and a method of producing it.

Metformin hydrochloride is a well known biguanide derivative (1,1-dimethylbiguanide monohydrochloride) which is widely used as oral antihtperglycemic agent in the management of noninsulin dependent diabetes mellitus (NIDDM).

Metformin hydrochloride being a highly water soluble drug (>300 mg/ml at 25°C), leads to the difficulty in making a sustained release dosage form.

Marketed preparations available earlier with 850 mg dose of metformin hydrochloride having label of retard tablets (Glucophase RTM retard) have not been able to demonstrate any advantage in a limited volunteer trials. This probably attributable to poor choice of polymers and low dosage, desired for sustained action.

US patent 5,955,106 by Moeckel, J. describes the process of making metformin hydrochloride 850 mg retard tablet containing hydrocolloid forming retarding agents and further control of release provided by film envelop. It

however does not provide any justification for using 850 mg dose of metformin hydrochloride for delayed release preparation and the expected release rates from such compositions. This patent also does not give any in-vitro and in-vivo data to support its claims. Literature survey indicates metformin hydrochloride has only 40% to 60% bioavailability with high renal clearance. Hence the dose 850 mg may be insufficient to achieve therapeutic plasma concentration, around 1 µg/ml for a sufficient period of time and might require to take such tablets twice or thrice a day.

WP patent 99/47128 by Timmins et al describes a biphasic controlled release delivery system for metformin hydrochloride with inner solid particulate phase and outer solid continuos phase utilizing hydrophilic and hydrophobic polymers. These tablets are hydrodynamicaly balanced and swells upto approximately three times its dry size following hydration However it is well documented that in supine position the tablet escapes through the pylorus of the stomach after administration, which may deteriorate the tablet's in-vivo performance. Also volume desired to maintain floating of the tablet is never enough in the stomach except in fed condition. Hence making such system is doubtful with reference to its performance. Another major limitation of this patent is about dosage of the metformin hydrochloride and formulation. For instance, examples cited provides formulation of 500 mg metformin hydrovchloride with tablet weight of approximately 1.0 gm . Hence restricting to the use of low dose sustained release tablets of 500 mg or slightly more only and making it obligatory to take two tablets of 500 mg each time to provide sustained action.

The present invention is based on the scientific calculation of dose of metformin hydrochloride desired, based on the data available from in-vivo studies which are well documented in the scientific literature. The model used here is based on the mathematical equations provided by Dobrinska and Welling (1975) which gives fairly accurate calculations about loading dose and maintenance dose for achieving sustained release effect.

The dose of metformin hydrochloride is calculated by considering the following pharmacokinetic values from the literature.

Plasma concentration Cmax = 1.02 µg/ml

Elimination half life t 1/2 = 6.2 hours.

Volume of disribution Vd = 275 litrs.

Renal clearance = 552± 139 Litrs/min.

Total clearance = 1300 ml/min.

Using Dobrinska and Welling model, the calculated loading dose is 283 mg and maintenance dose is 759 mg and the total dose is 1040 mg of metformin hydrochloride for achieving sustained release effect for 24 hours.

The object of the present invention is to prepare palatable and swallowable pharmaceutical preparation containing as high as approximately 1.0 gm metformin by suitable technology showing demonstrable release rate and facilitated in-vivo absorption for the desired period. The emphasis is to develop simple monolithic system composed of hydrophobic polymers and other excepients with improved kinetics of extended release dosage forms and with highest possible content of active substance and the simplest method of producing it.

The monolithic sustained release system of the invention is a homogeneous system composed of active drug in an amount within the range of 60 to 90% by weight, preferably 70 to 80% by weight, and one or more hydrophobic polymers or one or more other type of hydrophobic materials. In an amount within the range of about 15 to 40% by weight, preferably 20 to 30 % by weight based on the weight of the active substance.

Hydrophobic polymers which may be employed for the monolithic sustained release system in the present invention include, but not limited to stearic acid, glycerylmonostearate, glyceryl behenate, glyceryl monooleate, glyceryl palmitostearate, microcrystalline wax, stearyl alcohol, cetyl alcohol, cetostearyl alcohol, hydrogenated castor oil, tristearin, waxes, polyethylene powder, polyvinyl chloride, shellac, rosin, and the like. Where the mixtures of the hydrophobic polymer will be employed in weight ratio to other hydrophobic material within the range of about 1: 0.01 to 1: 5 , preferably about 1 : 0.3

The pharmaceutical compositions according to the present invention can be used to produce compressed tablets of any shape, preferably oval shape and can be additionally provided with film coat of commonly used hydrophilic coating polymers. The film envelop used cane a taste neutralizing film forming agent to which dies can optionally be added can be used for elegance. The proportion by weight of the film envelop relative to the final tablet is in the usual range of 0.5 to 4.0% by weight preferably 1.0 to 1.5% by weight. Film formers such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, starch, cellulose derivatives and the like.

The monolithic composition according to the present invention can also be used to produce compressed slugs and filled into capsules.

Auxiliary substances which may be employed for monolithic sustained release system in the present invention include, binder, like polyvinyl pyrrolidone, gelatin, gum acacia, Klucel EF (hydroxypropyl cellulose), carboxymethyl cellulose sodium, etc.; Where as the glidants include, but not limited to colloidal siliconedioxide, talc, starch, and the like; lubricants include, but not limited to magnesium stearate, zinc stearate, and the like

The pharmaceutical dosage form according to the present invention such as tablet, apart from active drug and hydrophobic polymers and or hydrophobic materials may contain 1.0 to 15 % by weight of a binder, preferably 3.0 to 10 % by weight ; and upto 2.0 % by weight of glidant preferably 0.5 to 1.0 5 by weight; and upto 2.0 % by weight of lubricants preferably 0.5 to 1.0 % by weight ; each in relation to the tablet weight.

In the present invention the pharmaceutical composition, such as tablets are produced by dry mixing of active substance and optionally further auxiliary substance and granulating this mixture with hydrophobic polymers and or other hydrophobic materials by hot melt granulation technique using jacketed rapid mixer granulator at a temperature 40 to 120 °C, preferably 60 to 80 °C. This is followed by gradually cooling the granulate mass to the room temperature with continuos mixing. The resulting mass is further granulated with aqueous or organic solution of the binder followed by drying and converting it into 30 µm to 2.0 mm granules, preferably 100 µm to 1.0 mm by

milling and sizing. Subsequently appropriate other pharmaceutical auxiliary substances are admixed with the sized granules.

In the present invention the pharmaceutical composition, such as tablets are also produced by dry mixing of active substance, optionally further auxiliary substances, hydrophobic polymers and or another hydrophobic materials and binder in extruder. This mixture is extruded at a temperature 40 to 120 °C , preferably 60 to 90 °C in a simple extruder used for injection molding of plastics, followed by extrusion of the melted homogeneous mass with gradual cooling to room temperature and converting into 30 to 2.0 µm to 2.0 mm granules, preferably 100 µm to 1.0 mm by milling and sizing. Subsequently appropriate other pharmaceutical auxiliary substances are admixed with the sized granules.

The composition produced in this manner is subsequently processed in the usual manner to produce pharmaceutical dosage forms, such as e.g. Compressed into tablets or filling of pressed slugs into capsule. The tablets can be coated with a film using the standard coating processes and methods such as conventional coating pan or fluid coating process.

The sustained release tablets according the present invention release metformin hydrochloride in a controlled manner which is suppose to provide an effect over a time period upto 24 hours, preferably over 18 hours as per the calculations.

Useful metformin sustained release formulations as per the invention shows the following in-vitro drug release characteristics when tested in gastric fluid pH 1.2 for first hour and then in phosphate buffer pH 6.8 USP.

Tim	% Release
1	38 – 45%
2	50 – 55 %
3	62 – 68 %
4	70 – 75 %
5	80 – 85 %
6	85 – 90 %
7	91 – 95 %
8	96 – 100 %

Example 1 :

225 gm of stearic acid was melted at 70°C temperature. 1000 gm metformin hydrochloride was heated to 70°C in a jacketed rapid mixer granulator and granulated with above melted stearic acid at 70°C temperature. After granulation the granulate mass was mixed continuously with gradual cooling to room temperature.

60 gm of shellac and 25 gm of polyvinyl pyrollidone were dissolved in 150 gm of isopropyl alcohol. This solution was gradually added to above metformin stearic acid granulate and mixed till dough mass formed. The resulting dough mass was dried at 45°C for 2 hours and then sized through 2.4 mm screen to break the agglomerates. These sized granules (1310 gm) were blended with 4.0 gm of colloidal silicone dioxide and 8.0 gm of magnesium stearate and compressed into capsule shape oval tablets of each containing 1000 mg of metformin hydrochloride.

The in-vitro release of metformin hydrochloride form these tablet was as follows.

Time (Hrs)	% Release
1	40 %
2	55 %
3	65 %
4	75 %
5	82 %
6	89 %
7	95 %
8	99.5 %

Example 2 :

225 gm of stearic acid , 1000 gm metformin hydrochloride, 60 gm of shellac and 25 gm of polyvinyl pyrollidone were mixed in the extruder at 70°C and extruded and then gradually cooled to room temperature. The resulting agglomerates were sized through 2.4 mm screen . These sized granules (1310 gm) were blended with 4.0 gm of colloidal silicone dioxide and 8.0 gm of magnesium stearate and compressed into capsule shape oval tablets of each containing 1000 mg of metformin hydrochloride.

The in-vitro release of metformin hydrochloride form these tablet was as follows

Time (Hrs)	% Release
1	42 %
2	57 %
3	68 %

4	77 %
5	84 %
6	90 %
7	96 %
8	100 %

Example 3 :

250 gm of glyceryl mono stearate was melted at 70°C temperature. 1000 gm metformin hydrochloride was heated to 70°C in a jacketed rapid mixer granulator and granulated with above melted stearic acid at 80°C temperature. After granulation the granulate mass was mixed continuously with gradual cooling to room temperature.

60 gm of shellac and 25 gm of polyvinyl pyrollidone were dissolved in 150 gm of isopropyl alcohol. This solution was gradually added to above metformin stearic acid granulate and mixed till dough mass formed. The resulting dough mass was dried at 45°C for 2 hours and then sized through 2.4 mm screen to break the agglomerates. These sized granules (1335 gm) were blended with 4.0 gm of colloidal silicone dioxide and 8.0 gm of magnesium stearate and compressed into capsule shape oval tablets of each containing 1000 mg of metformin hydrochloride.

The in-vitro release of metformin hydrochloride form these tablet was as follows.

Tim (Hrs)	% Release
1	39 %
2	52 %
3	61 %
4	72 %
5	80 %
6	88 %
7	94 %
8	98 %

Example 4 :

175 gm of polyethylene powder , 1000 gm metformin hydrochloride and 25 gm of polyvinyl pyrollidone were mixed in the extruder at 70°C and extruded and then gradually cooled to room temperature. The resulting agglomerates were sized through 2.4 mm screen . These sized granules (1200 gm) were blended with 4.0 gm of colloidal silicone dioxide and 8.0 gm of magnesium stearate and compressed into capsule shape oval tablets of each containing 1000 mg of metformin hydrochloride.

The in-vitro release of metformin hydrochloride form these tablet was as follows.

Time (Hrs)	% Release
1	48 %
2	54.2 %

3	64 %
4	73.4 %
5	82 %
6	90.3 %
7	96 %
8	99.7 %

Example 5 :

160 gm of polyvinyl chloride powder , 1000 gm metformin hydrochloride and 25 gm of polyvinyl pyrollidone were mixed in the extruder at 70°C and extruded and then gradually cooled to room temperature. The resulting agglomerates were sized through 2.4 mm screen . These sized granules (1185 gm) were blended with 4.0 gm of colloidal silicone dioxide and 8.0 gm of magnesium stearate and compressed into capsule shape oval tablets of each containing 1000 mg of metformin hydrochloride.

The in-vitro release of metformin hydrochloride form these tablet was as follows.

Time (Hrs)	% Release
1	42 %
2	53.1 %
3	62,5 %
4	72 %
5	80 %
6	85 %
7	94 %
8	98.8 %

Example 6 :

230 gm of hydrogenated castor oil was melted at 70°C temperature. 1000 gm metformin hydrochloride was heated to 70°C in a jacketed rapid mixer granulator and granulated with above melted stearic acid at 70°C temperature. After granulation the granulate mass was mixed continuously with gradual cooling to room temperature.

60 gm of shellac and 25 gm of polyvinyl pyrollidone was dissolved in 150 gm of isopropyl alcohol. This solution was gradually added to above metformin stearic acid granulate and mixed till dough mass formed. The resulting dough mass was dried at 45°C for 2 hours and then sized through 2.4 mm screen to break the agglomerates. These sized granules (1315 gm) were blended with 4.0 gm of colloidal silicone dioxide and 8.0 gm of magnesium stearate and compressed into capsule shape oval tablets of each containing 1000 mg of metformin hydrochloride.

The in-vitro release of metformin hydrochloride form these tablet was as follows.

Time (Hrs)	% Release
1	41 %
2	53 %
3	66 %
4	74.9 %
5	83 %
6	91 %
7	96.2%
8	100 %

References :

1. Moeckel, J., Gabel, R., Woog, H., [1997] , U.S. Patent 5,955,106.
2. Timmins, P., Vyas, K., [1999] , World Patent WO 99/47128.
3. Noel, M., (1980) , Jounal of International Biomedical Information and Data (IBID), 1 (1) , 9 – 20.
4. Kenneth, C., Ralph, A. D., (1998) , Diabetes Reviews, 6 (2) , 89 – 131.
5. Nancy C. Sambol, Jaine Chaing, Michael O'Conner, Chui Y. Liu, (1196), J. Clin. Pharmacol., 36 , 1012 –1021.
6. Physician Desk reference, Edition 58, (2000), Medical economic company Inc. NJ 07645-1742, Glucophase® , page 831–835.

CLAIMS :

1. Monolithic pharmaceutical composition comprising metformin hydrochloride as the active substance and hydrophobic polymer and or other hydrophobic material.
2. Composition of claim 1, wherein the sustained release dose for metformin hydrochloride is at least 1000 mg.
3. Composition of claim 1, wherein at least 74 % by weight of the composition is metformin hydrochloride.
4. The pharmaceutical formulation as defined in claim 1, wherein the hydrophobic polymer and or hydrophobic material is selected from the group consisting of Fatty acids, Fatty alcohols, Fatty acid esters, Hydrogenated oils, waxes and natural resins.
5. Composition of claim 4, wherein the hydrophobic polymer and or hydrophobic material comprises stearic acid, glyceryl monostearate, glyceryl behenate, glyceryl pamitostearate, glyceryl monooleate, microcrystalline wax, stearyl alcohol, cetyl alcohol, cetostearyl alcohol, hydrogenated castor oil, tristearin, shellac, rosin, polyvinyl chloride powder, polyethylene powder, and the like.
6. Composition of claim 1, further comprising about 3 to 10% by weight binder, up to 0.5 to 1.5% by weight glidant and up to 0.5 to 1.0% by weight of the lubricant.
7. Composition of claim 1, wherein pharmaceutical composition is tablet.

8. Process of producing a sustained release metformin hydrochloride composition of claim 1 which can be compresses comprising :

   i) Granulating metformin hydrochloride and hydrophobic polymer and or other hydrophobic material by hot melt granulation or by extrusion.

   ii) And drying the granulated product.

9. Process of claim 8, wherein the aqueous or organic solvent used in the granulation step contains a binder.

10. Process of claim 8, including the further step of compressing the dried granulated product into tablets.

11. Process of claim 10, including the further step of coating the tablet with a film envelope for taste neutralization.

12. Process of claim 10, wherein the compacted product further includes up to 1.5% by weight of lubricant, upto 1% by weight of glidant, and up to 4.5%by weight of binder.

13. The pharmaceutical composition according to claim 1 which releases metformin hydrochloride in a controlled and reproducible manner right from start and in the duration of minimum 8 hours.

14. The pharmaceutical composition of claim 1, used as oral antihtperglycemic agent in the management of noninsulin dependent diabetes mellitus (NIDDM).

* * * * *

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB00/01404

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A01N 37/52; A61K 47/30, 9/20, 9/22, 9/28
US CL : 514/635, 772.3; 424/464, 465, 468, 474

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/635, 772.3; 424/464, 465, 468, 474

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/47128 A1 (BRISTOL-MYERS SQUIBB COMPANY) 23 September 1999, See entire document.	1-14
Y	US 5,922,769 A (BARELLI et al.) 13 July 1999, See entire document.	1-14
Y	US 6,011,049 A (WHITCOMB) 04 January 2000, See entire document.	1-14
Y	US 6,099,859 A (CHENG et al.) 08 August 2000, See entire document.	1-14
Y	US 6,099,862 A (CHEN et al.) 08 August 2000, See entire document.	1-14
Y	US 6,117,451 A (KUMAR) 12 September 2000, See entire document.	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 16 JANUARY 2001	Date of mailing of the international search report 09 MAY 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer LILIANA DI NOLA-BARON Telephone No. (703) 308-12

TERRY J. DEY
PARALEGAL SPECIALIST
TECHNOLOGY CENTER 1600

Form PCT/ISA/210 (second sheet) (July 1998) *

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

Internat al Application No
PCT/CA 98/00274

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 000 962 A (SANGEKAR ET AL.) 19 March 1991 see column 6; example 3 ---	1,2,5, 10,11, 16,27,28
X	EP 0 226 884 A (COLOMBO ET AL.) 1 July 1987 see page 10 - page 12; example 1 ---	1,2,5, 10, 16-18,29
X	DATABASE WPI Week 9142 Derwent Publications Ltd., London, GB; AN 91-307312 XP002079685 & JP 03 206039 A (KYOTO PHARM IND CO LTD) , 9 September 1991 see abstract --- -/--	1-3,5, 10,12, 13,16,29

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 October 1998	15/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/CA 98/00274

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 253 490 A (MERCK & CO) 20 January 1988 see page 8; example 3 see claims 1-3,5-7	1-3
X	EP 0 157 695 A (FOREST LABORATORIES, INC.) 9 October 1985 see page 19 - page 20; examples 3,4	1-3,8
Y	US 5 015 479 A (MULLIGAN ET AL.) 14 May 1991 see column 6; example 10	4
Y	US 5 451 409 A (RENCHER ET AL.) 19 September 1995 see claim 1	4
A	EP 0 468 436 A (SS PHARMACEUTICAL CO., LTD.) 29 January 1992 see page 12; example 7	23
A	SHAN-YANG LIN ET AL.: "water uptake and drug release behaviour of drug-loaded compacts prepared from different grades of ethylcellulose" EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, vol. 42, no. 3, June 1996, pages 193-198, XP000589998 Amsterdam (NL) see the whole document	23

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern: al Application No
PCT/CA 98/00274

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5000962 A	19-03-1991	NONE	
EP 226884 A	01-07-1987	AU 594992 B	22-03-1990
		AU 6672586 A	25-06-1987
		CA 1298479 A	07-04-1992
		JP 2535339 B	18-09-1996
		JP 62155211 A	10-07-1987
		US 4839177 A	13-06-1989
EP 253490 A	20-01-1988	AU 597670 B	07-06-1990
		AU 7422887 A	17-12-1987
		CY 1578 A	20-12-1991
		DK 170514 B	09-10-1995
		HK 56191 A	26-07-1991
		IE 60508 B	27-07-1994
		JP 1715235 C	27-11-1992
		JP 4000045 B	06-01-1992
		JP 63054319 A	08-03-1988
		KR 9502882 B	28-03-1995
		PT 85049 B	08-03-1990
		US 4900755 A	13-02-1990
		US 4983400 A	08-01-1991
		ZA 8704233 A	14-12-1987
EP 157695 A	09-10-1985	US 4795327 A	03-01-1989
		CA 1240925 A	23-08-1988
		DE 3583694 A	12-09-1991
		DK 136385 A,B,	27-09-1985
		JP 60218329 A	01-11-1985
		US 4849229 A	18-07-1989
US 5015479 A	14-05-1991	NONE	
US 5451409 A	19-09-1995	NONE	
EP 468436 A	29-01-1992	JP 2572673 B	16-01-1997
		JP 4082825 A	16-03-1992
		CA 2046845 A	26-01-1992
		DE 69128569 D	12-02-1998
		DE 69128569 T	16-04-1998

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter nal Application No
PCT/CA 98/00274

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 468436 A		ES 2111547 T	16-03-1998
		US 5164193 A	17-11-1992